# Optimization of GPR40 Agonists for Type 2 Diabetes

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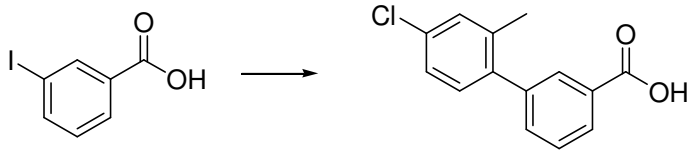
## Supporting Information

**Abbreviations of the solvents and reagents:** CDCl3, deuterochloroform; DMSO-d6, hexadeuterodimethyl sulfoxide; EtOAc, ethyl acetate; MeOH, methanol; EtOH, ethanol; i-PrOH (IPA), 2-propanol; DMF, N,N-dimethylformamide; DMSO, dimethyl sulfoxide; THF, tetrahydrofuran; $Et_2O$, diethyl ether; DME, 1,2-dimethoxyethane; CAN, MeCN or $CH_3CN$, acetonitrile; DCM or $CH_2Cl_2$, dichloromethane; LiOH, Lithium hydroxide; $NH_4Cl$, ammonium chloride; $NaHCO_3$, sodium hydrogen carbonate; $MgSO_4$, magnesium sulfate; $Na_2SO_4$, sodium sulfate; $K_2CO_3$, potassium carbonate; $Cs_2CO_3$, cesium carbonate; Pd-C, palladium on carbon; $Et_3N$ or TEA, triethylamine; HCl, hydrochloric acid; AcOH, acetic acid.

**General chemistry:** All reactions were conducted under an inert gas atmosphere (nitrogen or argon) using a Teflon-coated magnetic stir bar at the temperature indicated. Commercial reagents and anhydrous solvents were used without further purification. Analytical thin layer chromatography (TLC) and flash chromatography were performed on Merck silica gel 60 (230-400 mesh). Removal of solvents was conducted by using a rotary evaporator, and residual solvent was removed from nonvolatile compounds using a vacuum manifold maintained at approximately 1 Torr. All yields reported are isolated yields. Product purification by flash chromatography was performed using Teledyne-ISCO Redisep normal phase silica gel columns on a Teledyne-ISCO Companion; or by preparative reversed-phase high pressure liquid chromatography (RP-HPLC) using an Agilent 1100 Series HPLC and Phenomenex Gemini C18 column (5 micron, 100 mm × 30 mm i.d.), eluting with a binary solvent system A and B using a gradient elusion [A: $H_2O$ with 0.1% trifluoroacetic acid (TFA); B: $CH_3CN$ with 0.1% TFA; standard method 10-95% A:B]

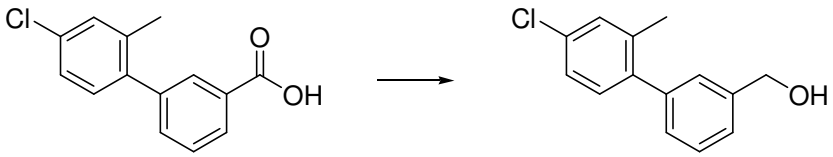
with UV detection at 220 nm. Low-resolution mass spectral (MS) data were determined on Agilent 1200 series LC connected to an Agilent 6140 quadrupole MS analyzer (ESI). High-resolution mass spectra (HRMS) were obtained on an Agilent 6510 Q-TOF MS with an Agilent 1200 LC on the front end. $^1$H NMR spectra were obtained on a Bruker Avance III 500 (500 MHz) or Bruker Avance II 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = single; d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, br = broad.

## Synthesis of Compound 3




**3.1**

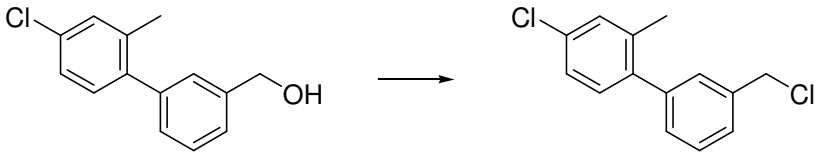
**4'-Chloro-2'-methyl-biphenyl-3-carboxylic acid (3.1).** To a mixture of 3-iodobenzoic acid (11.9 g, 48 mmol), 4-chloro-2-methylphenylboronic acid (9.8 g, 57.7 mmol) and sodium carbonate (6.1 g, 57.7 mmol) under nitrogen atmosphere, was added i-PrOH-water (1/1, 180 mL) followed by 10% Pd-C (2 g, 19.2 mmol) with caution. The reaction mixture was heated at 80 °C under nitrogen overnight. The catalyst was removed by filtration, and the filtered catalyst was washed with EtOH (60 mL). Most of organic solvent was removed under reduced pressure. The resulting aqueous residue was treated with 2N HCl (aq) to bring the pH < 2. The resulting mixture was extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with water and saturated brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Compound **3.1** was obtained as white solid (12 g, 84%), which was used directly in the next step. MS ESI (neg.) m/e: 245 (M-H).




**3.1** **3.2**

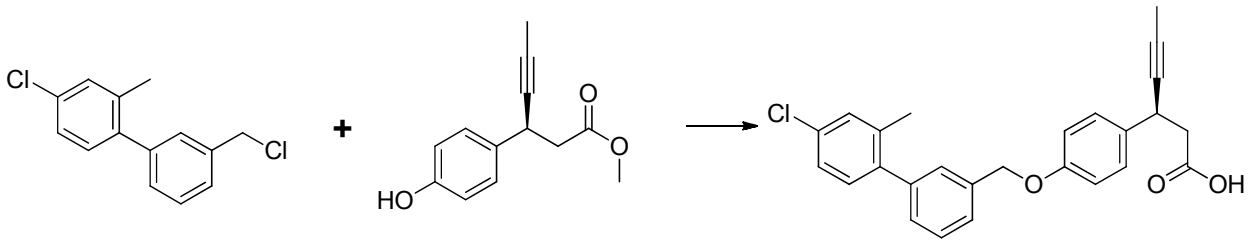
**4'-Chloro-2'-methyl-biphenyl-3-yl)-methanol (3.2).** $LiAlH_4$ (1.0 M in THF, 50 mL, 50 mmol) was added slowly to solution of **3.1** (6.0 g, 24.4 mmol) in THF (40 mL) *via* syringe at 0 °C,

under nitrogen atmosphere. The reaction mixture was brought to room temperature by stirring overnight. The reaction mixture was quenched with cold water with caution. The reaction mixture was filtered through a short pad of silica gel after treating with Celite® (6 g). The filtered solid cake was washed with EtOAc (150 mL). The combined organic extracts were concentrated under reduced pressure and re-dissolved in EtOAc (150 mL). The resulting organic solution was washed with NaOH (10% in water, 30 mL), water and saturated brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Compound **3.2** was obtained as colorless oil (5.4 g, 95%) which was used directly in the next step. LC-MS ESI (pos.) m/e: 233 (M+H), 215(M+H-$H_2O$).




**3.2** **3.3**

**4-Chloro-3'-chloromethyl-2-methyl-biphenyl (3.3).** $SOCl_2$ (12 mL) was added slowly to a solution of **3.2** (5.4 g, 23.2 mmol) in DCM (100 mL) *via* syringe at 0 °C, under nitrogen atmosphere. The reaction mixture was brought to room temperature by stirring overnight. The solvent was removed under reduced pressure, and the residue was flash chromatographed (silica gel, 0-5% EtOAc in hexane). Compound **3.3** was obtained as colorless oil (5.2 g, 89%). LC-MS ESI (pos.) m/e: 251 (M+H), 215(M+H-HCl). $^1$H NMR (500 MHz) ($CDCl_3$) δ 7.17-7.44 (m, 7H); 4.65 (s, 2H); 2.27 (s, 3H).



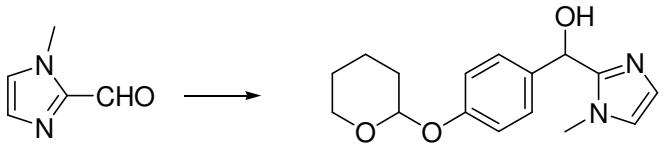

**3.3** **2.1** **3**

**(*S*)-3-(4-((4'-Chloro-2'-methyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)hex-4-ynoic acid (3)**. To a 10-mL round-bottomed flask was added **2.1** (150 mg, 0.687 mmol), **3.3** (201 mg, 0.800 mmol) and cesium carbonate (260 mg, 0.798 mmol) in DMF (2 ml). The reaction mixture was stirred at 23 °C utill the reaction went to completion by LCMS. The reaction mixture was diluted with

water (20 mL) and extracted with EtOAc ( 2 x 30 mL). The organic extract was washed with saturated aquous NaCl (40 mL) and dried over $Na_2SO_4$. The solution was filtered and concentrated in vacuo to give the crude material as a light-yellow solid. LCMS (pos) $[M+H]^+$: 433.

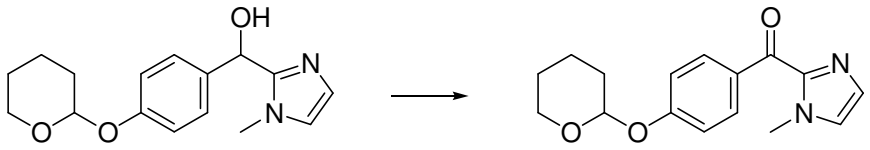
The above crude product (S)-methyl 3-(4-((4'-chloro-2'-methyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)hex-4-ynoate was dissolved in 2 mL of EtOH and treated with 10% NaOH water solution (1.5 mL) at 0 °C. The reaction mixture was stirred at 0 to 23 °C overnight and the reaction was complete by LCMS. The reaction mixture was acidified by hydrochloric acid, 2N (3 ml, 6.00 mmol). The solvent was removed in vacuo and the residue was re-dissolved in DMF/MeCN and purified by reverse-phase preparative HPLC using a C18 column, 0.1% TFA in $CH_3CN/H_2O$, gradient 5% to 95% over 30 min to provide compound **3** (260 mg, 90 % yield, two steps) as a colorless film. LCMS (neg) $[M-H]^-$: 417. $^1H$ NMR (500 MHz, $CDCl_3$) δ ppm 7.39 - 7.46 (m, 2 H), 7.21 - 7.35 (m, 6 H), 7.13 - 7.18 (m, 1 H), 6.94 - 6.96 (m, 1 H), 6.94 (s, 1 H), 5.10 (s, 2 H), 4.07 (ddd, J=8.50, 6.42, 2.45 Hz, 1 H), 2.82 (dd, J=15.65, 8.56 Hz, 1 H), 2.72 (dd, J=15.65, 6.60 Hz, 1 H), 2.23 (s, 3 H), 1.84 (d, J=2.45 Hz, 3 H). HRMS (TOF) Calculated for $C_{26}H_{24}ClO_3^+$ $[M+H]^+$: 419.1408, found: 419.1414.

## Synthesis of Compound 4



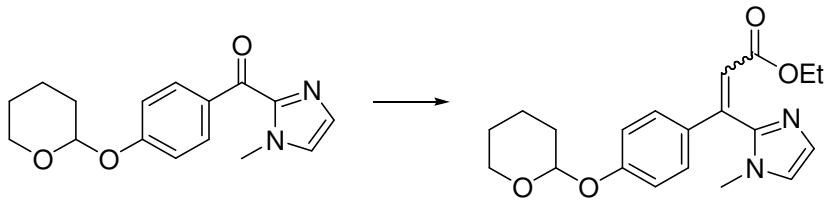

**4.1**

**(1-Methyl-1H-imidazol-2-yl)(4-(tetrahydro-2H-pyran-2-yloxy)phenyl)methanol (4.1).** 4-(2-Tetrahydro-2H-pyranoxy)phenylmagnesium bromide (0.5M in THF, 160 mL, 80 mmol) was added slowly to a solution of 1-methyl-2-imidazolecarboxaldehyde (8 g, 72.7 mmol) in THF (100 mL) *via* syringe at –78 °C. The reaction mixture was stirred at this temperature for 3 hours and quenched with saturated $NH_4Cl$ (aq). The mixture was extracted with EtOAc (2 x 100 mL), and the combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to afford **4.1** as a colorless oil (21 g, 100%), which was used directly in the next step.



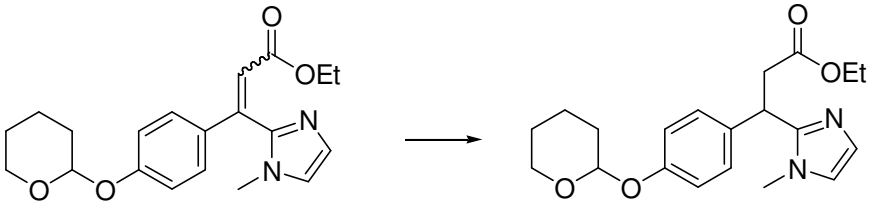
**4.1** **4.2**

**(1-Methyl-1H-imidazol-2-yl)(4-(tetrahydro-2H-pyran-2-yloxy)phenyl)methanone (4.2).** Pyridinium dichromate (36 g, 95.7 mmol) was added to a solution of **4.1** (21 g, 72.7 mmol) in DCM (100 mL) at 0 °C in several portions. The mixture was stirred at 0 °C for 1 hour and at room temperature for 6 hours. Silica gel (75 g) was added to the reaction mixture, and the resulting slurry was filtered through a pad of silica gel. The solid was washed with DCM (200 mL). The filtrate was washed with water and saturated brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give an oily residue, which was flash chromatographed (silica gel, 0-30% EtOAc in hexane) to afford ketone **4.2** as yellow solid (16 g, 76%). $^1$H NMR (500 MHz) ($CDCl_3$) δ 8.33-8.35 (m, 2H); 7.10-7.29 (m, 4H); 5.56 (t, J= 3.0 Hz, 1H); 4.08 (s, 3H); 3.85-3.90 (m, 1H); 3.61-3.65 (m, 1H); 2.03 (m, 1H); 1.90-1.91 (m, 2H); 1.69-1.74 (m, 2H); 1.61-1.64 (m, 1H).



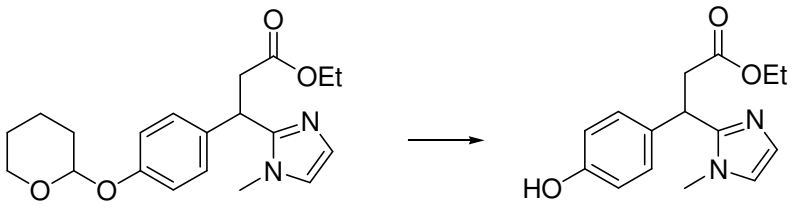
**4.2** **4.3**

**(Z/E)-Ethyl 3-(1-methyl-1H-imidazol-2-yl)-3-(4-(tetrahydro-2H-pyran-2-yloxy)phenyl)acrylate (4.3).** A solution of lithium hexamethyldisilazide (1M in THF, 64 mL) was added slowly to a stirred solution of ethyl (trimethylsilyl)acetate (9.9 g, 61.5 mmol) and ketone **4.2** (16 g, 55.9 mmol) in anhydrous THF (60 mL) *via* syringe at –78 °C. The reaction mixture was stirred at this temperature for 2 hours. The reaction temperature was allowed to rise to –20 °C over 6 hours. The reaction mixture was quenched with saturated ammonium chloride (aq) at this temperature, extracted with EtOAc (2 x 150 mL), and dried over $Na_2SO_4$. After filtration, the solvent was removed under reduced pressure to afford **4.3** as a colorless oil (21 g, including some ethyl (trimethylsilyl)acetate), which was used directly in the next step. LC-MS ESI (pos.) m/e: 357 (M+H).



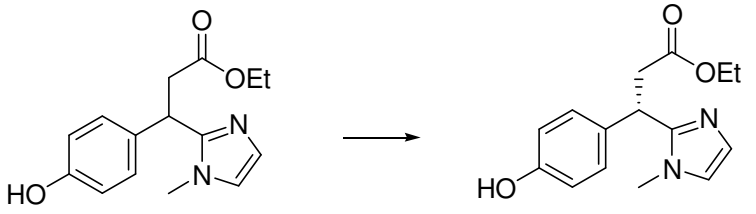
**4.3** **4.4**

**(+/-)-Ethyl 3-(1-methyl-1H-imidazol-2-yl)-3-(4-(tetrahydro-2H-pyran-2-yloxy)phenyl)propanoate (4.4).** A solution of olefin **4.3** (21 g, 55.9 mmol) in EtOH (200 mL) was stirred with 10% Pd-C (2.1 g, 2 mmol) under a hydrogen atmosphere (provided by a balloon) at room temperature overnight. The reaction mixture was filtered through a silica gel pad and concentrated to provide protected ester **4.4** as an off-white oil (21g), which was used directly in the next step. LC-MS ESI (pos.) m/e: 359 (M+H).



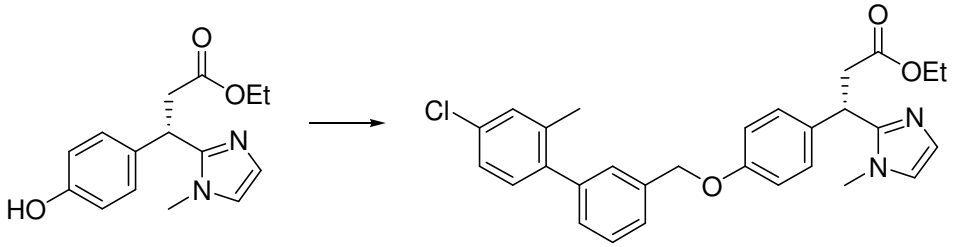
**4.4** **4.5**

**(+/-)-Ethyl 3-(4-hydroxyphenyl)-3-(1-methyl-1H-imidazol-2-yl)propanoate (4.5).** Trifluoroacetic acid (21 mL) was added to a solution of protected ester **4.4** (21g) in dry DCM (210 mL) with caution at 0 $^{o}$C. The mixture was brought to room temperature over 4 hours. The reaction mixture was concentrated under reduced pressure to provide a yellow oily residue, which was re-dissolved in DCM (200 mL) and washed with water, saturated $NaHCO_3$, water and brine, and dried over $Na_2SO_4$. After filtration, the solvent was removed under reduced pressure, and the product was crystallized in EtOAc-hexane. The mother liquid was concentrated and flash chromatographed (silica gel, 50% EtOAc in hexane as eluant). The product, (±)-ethyl 3-(4-hydroxyphenyl)-3-(1-methyl-1H-imidazol-2-yl)propanoate (**4.5**) was obtained as a colorless crystal (combined yield 11 g, 72% ,three steps). LC-MS ESI (pos.) m/e: 275 (M+H). $^1$H NMR (500 MHz) ($CDCl_3$) δ 9.28 (s, 1H); 6.98-7.00 (m, 3H); 6.65-6.77(m, 3H); 4.41 (dd, J=9.0, 3.0 Hz, 1H); 3.96 (q, J=7.0, 2H); 3.39 (s, 3H); 3.19 (dd, J=16.0, 7.0 Hz, 1H); 2.78 (dd, J= 16.0, 6.5 Hz, 1H); 1.80 (t, J= 7.0 Hz, 3H).



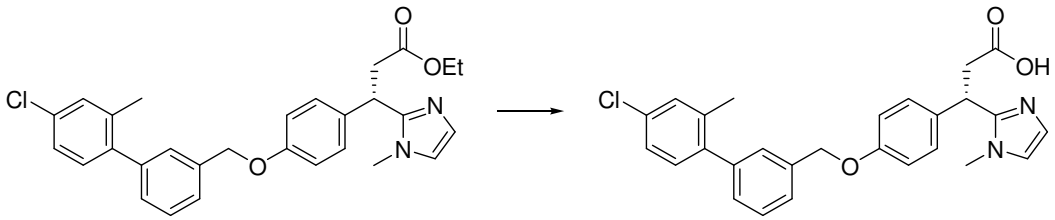
**4.5** **4.6**

**(*S*)-Ethyl 3-(4-hydroxyphenyl)-3-(1-methyl-1H-imidazol-2-yl)propanoate (4.6).** Racemic compound **4.5** was separated on a preparatory chiral HPLC with CHIRALPAK AD column, using 11% i-PrOH in hexane as eluant. Eluant containing the peak with greater retention time was concentrated and compound **4.6** (45%) was obtained as colorless crystals. The absolute configuration was assigned by analogy to other GPR40 agonist compounds.



**4.6** **4.7**

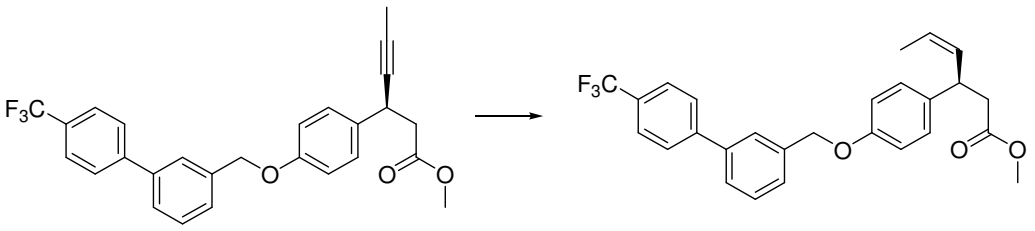
**(*S*)-3-[4-(4'-Chloro-2'-methyl-biphenyl-3-ylmethoxy)-phenyl]-3-(1-methyl-1H-imidazol-2-yl)-propionic acid ethyl ester (4.7).** $Cs_2CO_3$ (72 mg, 0.22 mmol) and compound **3.3** (53 mg, 0.21 mmol) were added successively to a solution of (*S*)-ethyl 3-(4-hydroxyphenyl)-3-(1-methyl-1H-imidazol-2-yl)propanoate (**4.6**) (55 mg, 0.2 mmol) in dry DMF (3 mL). The reaction mixture was stirred at room temperature overnight, diluted with EtOAc (60 mL), washed with water and brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum. The residue was flash chromatographed on silica gel (0-5% MeOH in DCM) to afford (*S*)-ethyl 3-(4-[3-(4-chloro-2-methylphenyl)benzyloxy]phenyl)-3-(1-methyl-1H-imidazol-2-yl)propanoate (**4.7**) as a colorless oil (97 mg, 99%). LC-MS ESI (pos.) m/e: 489 (M+H).



**4.7** **4**

**(*S*)-3-[4-(4'-Chloro-2'-methyl-biphenyl-3-ylmethoxy)-phenyl]-3-(1-methyl-1H-imidazol-2-yl)-propionic acid (4).** 10% NaOH (aq) (1 mL) was added to a solution of (*S*)-ethyl 3-(4-[3-(4-chloro-2-methylphenyl)benzyloxy] phenyl)-3-(1-methyl-1H-imidazol-2-yl)propanoate (**4.7**) (49 mg, 0.1 mmol) in EtOH (2 mL). The reaction mixture was stirred at room temperature for 4 hours. 1N HCl was added to neutralize the mixture to pH 6-7. The mixture was extracted with EtOAc (2 x 20 mL), washed with water and brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was flash chromatographed (silica gel, 0-10% MeOH in DCM) to afford (*S*)-3-[4-(4'-chloro-2'-methyl-biphenyl-3-ylmethoxy)-phenyl]-3-(1-methyl-1H-imidazol-2-yl)-propionic acid (**4**) as a colorless oil (43 mg, 93%). MS ESI (neg.) m/e: 459 (M-H). $^1$H NMR (500 MHz) (DMSO) δ 7.87 (broad s, 1H); 6.63-7.46 (m, 13H); 5.06 (s, 2H); 4.49 (dd, J=8.4, 3.2 Hz, 1H); 3.39 (s, 3H); 3.29 (dd, J=15.0, 8.5 Hz, 1H); 3.10 (dd, J=15.2, 3.0 Hz, 1H); 2.23 (s, 3H). HRMS (TOF) Calculated for $C_{27}H_{26}ClN_2O_3^+$ $[M+H]^+$: 461.1626, found: 461.1625.

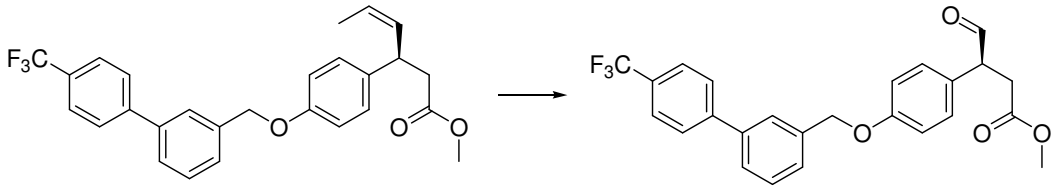
## Synthesis of Compound 5




**5.1** **5.2**

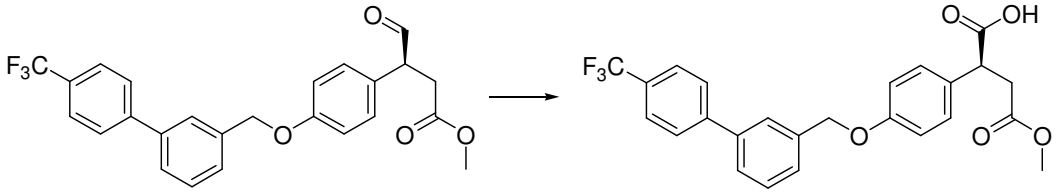
**Alkene (5.2).** Compound **5.1** (5.5 g, 12.16 mmol, experimental procedure was reported in supplemental material for reference 14 in this manuscript) was dissolved in 100 mL of EtOAc and quinoline (2 mL, 1.093 g/mL, 16.93 mmol) was added and nitrogen was bubbled through the solution for 5 minutes. 500 mg of Lindlar's catalyst was added, and a hydrogen balloon was attached. After 8 hours, the mixture was filtered through a plug of silica with EtOAc. The organic layer was washed with 2 N HCl (aq) (2 x 50 mL), saturated $NaHCO_3$ (aq) (1 x 50 mL), brine (1 x 50 mL) and dried with $MgSO_4$. The organic layer was filtered and concentrated under

reduced pressure. The material was chromatographed on silica with 10% EtOAc/hexane to afford **5.2** (5.1 g, 11.22 mmol, 92%) as a colorless oil. MS ESI (pos.) m/e: 455.0 $(M+H)^+$.



**5.2** **5.3**

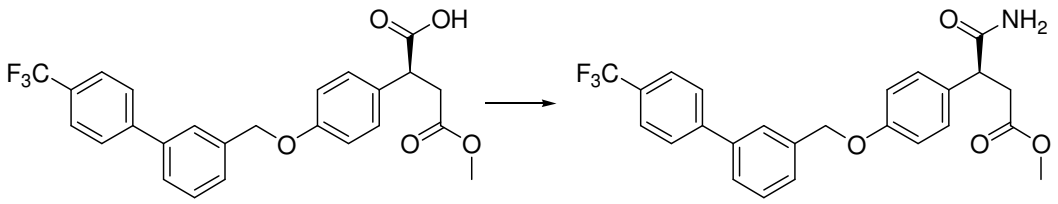
**Aldehyde (5.3).** Alkene **5.2** (5.1 g, 11.22 mmol) was dissolved in 100 mL of 4:1 (1,2-dioxane / water), and 2,6-lutidine (2.61 mL, 0.920 g/mL, 22.44 mmol) was added. Next, 1.2 g of a 3.4% $OsO_4$ in tBuOH (0.22 mmol) solution was added dropwise over 5 minutes. $NaIO_4$ (9.6 g, 44.88 mmol) in 25 mL of water was added. The internal reaction temperature did not rise above 30 °C. After 8 hours at room temperature, the reaction mixture was diluted with 500 mL of DCM, the layers were separated, and the organic layer was washed with 0.5 M $HCl_{(aq)}$ (2 x 50 mL), saturated $NaHCO_3$ (aq) (1 x 50 mL), 5% sodium sulfite (aq) (1 x 50 mL), and brine. The organic layer was dried with $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was flashed on silica with 30% EtOAc/hexanes to afford **5.3** (4.0 g, 9.09 mmol, 81%) as a yellow oil. MS ESI (pos.) m/e: 443.4 $(M+H)^+$.



**5.3** **5.4**

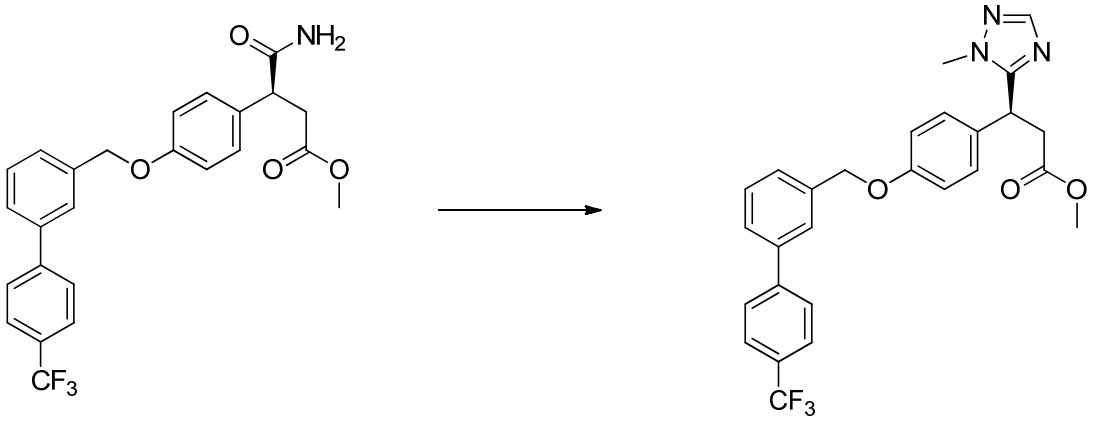
**Acid (5.4).** Aldehyde **5.3** (2.32 g, 5.25 mmol) was dissolved in 20 mL of acetonitrile. To this was added $KH_2PO_4$ (178 mg, 1.31 mmol) in 5 mL of water. The solution was cooled to –5 °C and 30% $H_2O_2$ (aq) (714 mg, 6.30 mmol) was added. $NaClO_2$ (712 mg, 7.88 mmol) was dissolved in 5 mL of water and added *via* syringe pump over 3 hours while maintaining a temperature below 0 °C. After the addition of the $NaClO_2$ solution, the mixture was stirred for 1 hour. 300 mL of DCM was added, and the pH of the aqueous layer was adjusted to 2 with 2 N HCl(aq). The aqueous layer was extracted with DCM (2 x 100 mL), and the combined organic extracts were washed with 5% sodium sulfite (aq) (1 x 50 mL), and brine. The organic layer was dried with $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was

chromatographed on silica with 50% EtOAc/hexanes to afford **5.4** (2.12 g, 4.62 mmol, 88%) as a colorless oil. MS ESI (pos.) m/e: 459.3 $(M+H)^+$.



**5.4** **5.5**

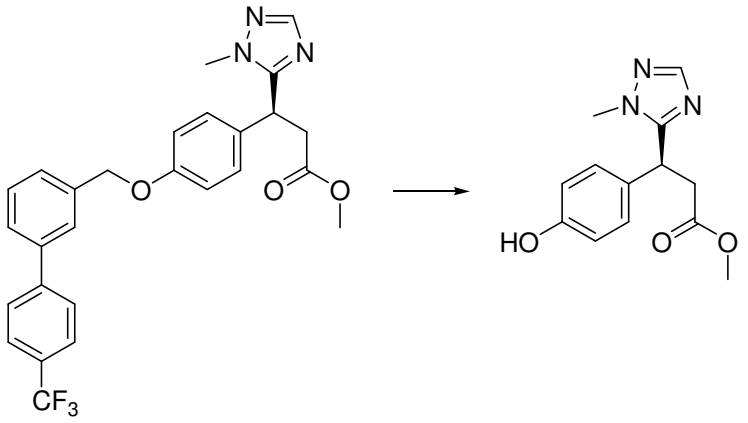
**Amide (5.5).** Acid **5.4** (6.0 g, 13.1 mmol) was dissolved in 100 mL of DCM. To this was added 1-hydroxybenzotriazole hydrate (3.7 g, 27.5 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbondiimide hydrochloride (5.0 g, 26.2 mmol), and 2M ammonia in n-PrOH (14 mL, 26.2 mmol). The reaction was stirred for 8 hours and diluted with 500 mL of EtOAc. The organic layer was washed with 2N HCl (aq) (2 x 75 mL), $NaHCO_3$ (aq) (1 x 75 mL), and brine (1 x 75 mL) and dried with $MgSO_4$ and filtered. The organic layer was concentrated under reduced pressure, and the residue was flashed through silica with 25% EtOAc/DCM. The combined fractions were concentrated under reduced pressure to afford **5.5** (5.3 g, 11.5 mmol, 88%) as a colorless oil.



**5.5** **5.6**

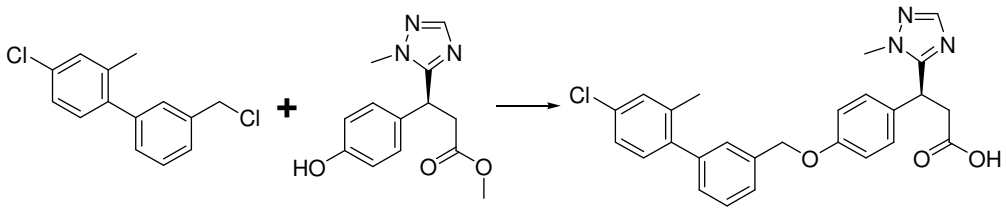
**(*S*)-3-(2-Methyl-2*H*-1,2,4-triazol-3-yl)-3-[4-(4'-trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-propionic acid (5.6).** Amide **5.5** (6.48 g, 14.2 mmol) was dissolved in 7 mL of N,N-dimethylformamide dimethyl acetal (119.17 MW, 0.894 g/mL, 52.6 mmol). The solution was gradually heated to 80 °C over 30 minutes. The mixture was allowed to cool to 35 °C, and the sample was concentrated under reduced pressure. The residue was dissolved in 20 mL of acetic acid followed by careful addition of methylhydrazine (5 mL, 0.866 g/mL, 94.0 mmol) over 5

minutes (the acid/base exotherm was used to run the reaction). The temperature increased to 65 °C, and an oil bath at 80 °C was used to finish the reaction. The total heating time was 45 minutes. The reaction was allowed to come to room temperature, and was diluted with 500 mL of DCM. The organic layer was washed with water (3 x 100 mL), brine (1 x 100 mL), dried with $Na_2SO_4$, filtered, and concentrated to a residue. The material was flashed on silica with 10% acetonitrile/DCM to afford methyltriazole **5.6** (4.3 g, 8.7 mmol, 61%) as a yellow oil. MS ESI (pos.) m/e: 496.5 $(M+H)^+$.



**5.6** **5.7**

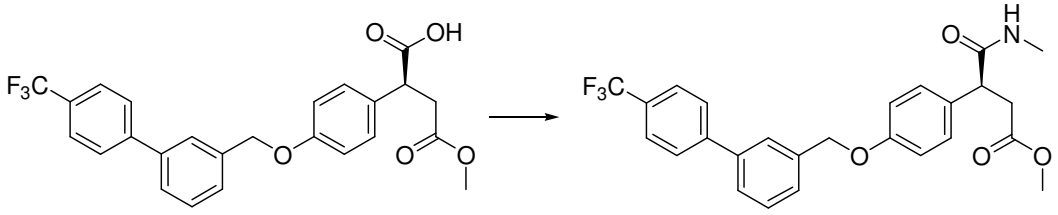
**(*S*)-Methyl 3-(4-hydroxyphenyl)-3-(2-methyl-2H-1,2,4-triazol-3-yl)propanoate (5.7).** Methyltriazole **5.6** (2.78 g, 5.61 mmol) was dissolved in 50 mL of EtOAc, and nitrogen was bubbled through the solution for 5 minutes. 1 g of palladium on carbon (5 wt. %, wet contains 50% water) was added, and a hydrogen balloon was attached. After 8 hours, the mixture was filtered through a plug of silica with 10% MeOH in EtOAc. The organic layer was concentrated under reduced pressure and partitioned between acetonitrile (100 mL) and hexane (50 mL). The acetonitrile layer was washed with hexane (4 x 50 mL). The acetonitrile layer was concentrated under reduced pressure to afford (S)-methyl 3-(4-hydroxyphenyl)-3-(2-methyl-2H-1,2,4-triazol-3-yl)propanoate **5.7** (1.30 g, 4.99 mmol, 89%) as a colorless oil. MS ESI (pos.) m/e: 262.4 $(M+H)^+$.



**3.3** **5.7** **5**

**(*S*)-3-[4-(4'-Chloro-2'-methyl-biphenyl-3-ylmethoxy)-phenyl]-3-(2-methyl-2*H*-1,2,4-triazol-3-yl)-propionic acid (5).** The phenol **5.7** (21 mg, 0.081 mmol) was dissolved in 1 mL of DMF and benzyl chloride **3.3** (22 mg, 0.089 mmol) was added followed by cesium carbonate (52 mg, 0.161 mmol). The reaction was stirred for14 hours and diluted with 50 mL of EtOAc. The organic layer was washed with 1N HCl (aq) (10 mL), saturated $NaHCO_3$ (aq) (10 mL), and brine (2 x 10 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in 2 mL THF and 0.11 N NaOH (aq) (1.1 mL, 0.12 mmol) was added. MeOH (1 mL) was added and the mixture became homogeneous. The solution was stirred for 8 hours and concentrated to remove the organic solvent. The slurry was dissolved in DMSO and the pH was brought to a pH of 2 with 2N HCl (aq). The material was chromatographed using HPLC. The combined fractions were combined and concentrated to afford methyltriazole **5** (22 mg, 0.049 mmol, 60%) as a colorless film. $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.68 (bs, 1H); 8.11 (s, 1H); 7.32-7.45 (m, 2H); 7.33 (s, 1H); 7.21-7.28 (m, 5H); 7.16 (d, J = 8.4 Hz, 2H); 6.97 (d, J = 8.7 Hz, 2H); 5.09 (s, 2H); 4.63 (dd, J = 4.9, 10.2 Hz, 1H); 3.83 (s, 3H); 3.54 (dd, J = 10.2, 17.4 Hz, 1H); 3.06 (dd, J = 4.9, 17.4 Hz, 1H); 2.23 (s, 3H).

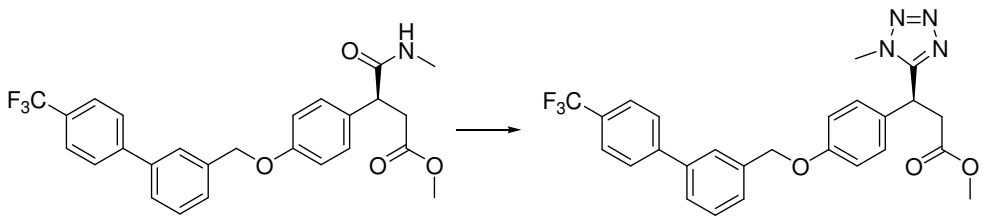
## Synthesis of Compound 6




**5.4** **6.1**

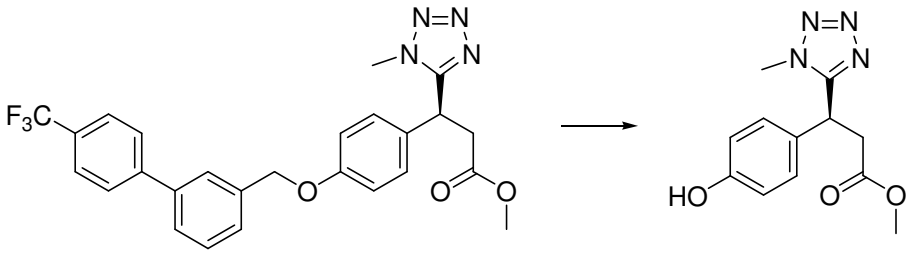
**Methylamide (6.1).** Acid **5.4** (6.0 g, 13.1 mmol) was dissolved in 100 mL of DCM. To this mixture was added 1-hydroxybenzotriazole hydrate (3.7 g, 27.5 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbondiimide hydrochloride (5.0 g, 26.2 mmol), and 2M methylamine in THF (14 mL, 26.2 mmol). The reaction was stirred for 8 hours, diluted with 500 mL of EtOAc, and the organic layer was washed with 2N HCl(aq) (2 x 75 mL), $NaHCO_3$ (aq) (1 x 75 mL), brine (1 x 75 mL) and dried with $MgSO_4$ and filtered. The organic layer was concentrated under reduced pressure, and the residue was flashed through silica with 15% EtOAc

/ DCM. The combined fractions were concentrated under reduced pressure to afford **6.1** (4.2 g, 11.5 mmol, 88%) as a colorless oil. MS ESI (pos.) m/e: 472.3 $(M+H)^+$.



**6.1** **6.2**

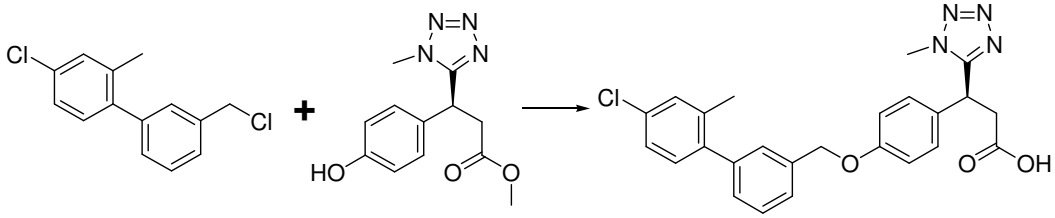
**(*S*)-3-(1-Methyl-1*H*-tetrazol-5-yl)-3-[4-(4'-trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-propionic acid (6.2).** Methylamide **6.1** (2.15 g, 4.59 mmol) was dissolved in 50 mL of acetonitrile. $NaN_3$ (900 mg, 13.8 mmol) was added followed by the dropwise addition of $Tf_2O$ (5.2 g, 18.4 mmol). The temperature rose to 34 °C. The reaction was stirred for 12 hours and diluted with 250 mL of DCM. The organic layer was washed with $NaHCO_3$ (aq) (2 x 50 mL), brine (1 x 50 mL) and dried with $MgSO_4$ and filtered. The organic layer was concentrated under reduced pressure, and the residue was flashed through silica with 15% EtOAc / DCM. The combined fractions were concentrated under reduced pressure to afford methyltetrazole **6.2** (1.52 g, 3.07 mmol, 67%) as a colorless oil. MS ESI (pos.) m/e: 497.4 $(M+H)^+$.



**6.2** **6.3**

**(*S*)-Methyl 3-(4-hydroxyphenyl)-3-(1-methyl-1H-tetrazol-5-yl)propanoate (6.3).** Methyltetrazole **6.2** (413 mg, 0.833 mmol) was dissolved in 5 mL of EtOAc and nitrogen was bubbled through the solution for 5 minutes. Palladium on carbon (200 mg, 5 wt. %, wet contains 50% water) was added, and a hydrogen balloon was attached. After 8 hours, the mixture was filtered through a plug of silica with 10% MeOH in EtOAc. The organic layer was concentrated under reduced pressure and partitioned between acetonitrile (10 mL) and hexane (5 mL). The acetonitrile layer was washed with hexane (4 x 5 mL). The acetonitrile layer was concentrated

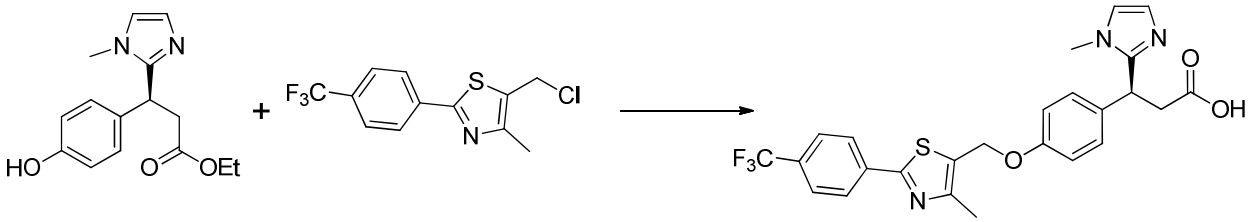
under reduced pressure to afford (*S*)-methyl 3-(4-hydroxyphenyl)-3-(1-methyl-1H-tetrazol-5-yl)propanoate (**6.3**) (203 mg, 0.775 mmol, 93%) as a colorless oil.



**3.3** **6.3** **6**

**(*S*)-3-[4-(4'-Chloro-2'-methyl-biphenyl-3-ylmethoxy)-phenyl]-3-(1-methyl-1*H*-tetrazol-5-yl)-propionic acid (6).** The phenol **6.3** (42 mg, 0.160 mmol) was dissolved in 1 mL of DMF and benzyl chloride **3.3** (45 mg, 0.176 mmol) was added followed by cesium carbonate (78 mg, 0.241 mmol). The reaction was stirred for 14 hours and diluted with 50 mL of EtOAc. The organic layer was washed with 1N HCl (aq) (10 mL), saturated $NaHCO_3$ (aq) (10 mL), and brine (2 x 10 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in 2 mL THF and 0.11 N NaOH (aq) (1.1 mL, 0.12 mmol) was added. MeOH (1 mL) was added, and the mixture became homogeneous. The solution was stirred for 8 hours and concentrated to remove the organic solvent. The slurry was dissolved in DMSO and the pH was brought to a pH of 2 with 2N HCl (aq). The material was chromatographed using HPLC. The combined fractions were concentrated to afford methyltetrazole **6** (59 mg, 0.128 mmol, 80%) as a colorless film. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38-7.43 (m, 2H); 7.31 (s, 1H); 7.19-7.26 (m, 4H); 7.13 (dd, J = 1.9, 8.3 Hz, 2H); 6.93 (d, J = 8.7 Hz, 2H); 5.07 (s, 2H); 4.55 (dd, J = 5.6, 9.4 Hz, 1H); 3.81 (s, 3H); 3.58 (dd, J = 9.4, 17.4 Hz, 1H); 3.05 (dd, J = 5.6, 17.4 Hz, 1H); 2.20 (s, 3H). HRMS (TOF) Calculated for $C_{25}H_{24}ClN_4O_3^+$ $[M+H]^+$: 463.1531, found: 463.1538.

## Synthesis of Compound 7

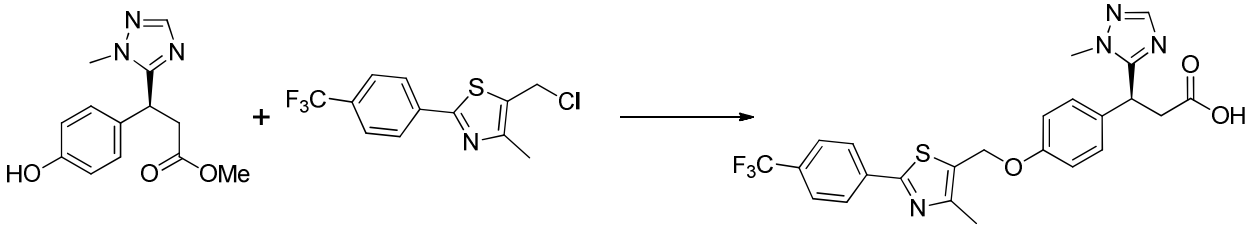


**4.6** **7**

**(*S*)-3-(1-methyl-1H-imidazol-2-yl)-3-(4-((4-methyl-2-(4-(trifluoromethyl)phenyl)thiazol-5-yl)methoxy)phenyl)propanoic acid (7)**. To a 10-mL round-bottomed flask was added (S)-ethyl 3-(4-hydroxyphenyl)-3-(1-methyl-1H-imidazol-2-yl)propanoate **4.6** (141 mg, 0.514 mmol), 5-(chloromethyl)-4-methyl-2-(4-(trifluoromethyl)phenyl)thiazole (181 mg, 0.620 mmol) and cesium carbonate (180 mg, 0.552 mmol) in DMF (2 ml). The reaction mixture was stirred at 23 °C till the reaction went to completion by LCMS. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 30 mL). The organic extract was washed with satd NaCl (30 mL) and dried over $Na_2SO_4$. The solution was filtered and concentrated in vacuo to give the crude product as a light-yellow solid. MS ESI (pos.) m/e: 530 $(M+H)^+$.

The above crude product (S)-ethyl 3-(1-methyl-1H-imidazol-2-yl)-3-(4-((4-methyl-2-(4-(trifluoromethyl)phenyl)thiazol-5-yl)methoxy)phenyl)propanoate was dissolved in 2 mL of EtOH and treated with 10% NaOH water solution at 0 °C. The reaction mixture was stirred at 0 to 23 °C overnight and the reaction was complete by LCMS. The reaction mixture was acidified by TFA/DCM (1/1). The solvent was removed in vacuo and the residue was re-dissolved in DMF/MeCN and purified by reverse-phase preparative HPLC (using a C18 column, 0.1% TFA in $CH_3CN/H_2O$, gradient 5% to 95% over 30 min) to provide compound **7** (150 mg, 0.299 mmol, 58 % yield) TFA salt as a off-white solid. LCMS (neg) m/e: 500 $(M-H)^-$. $^1H$ NMR (500 MHz, DMSO-$d_6$) d ppm 2.47 (s, 3 H) 3.10 (dd, *J*=17.24, 6.24 Hz, 1 H) 3.48 (dd, *J*=17.12, 9.78 Hz, 1 H) 3.80 (s, 3 H) 4.92 (dd, *J*=9.54, 6.36 Hz, 1 H) 5.34 (s, 2 H) 7.07 (m, *J*=8.56 Hz, 2 H) 7.36 (m, *J*=8.80 Hz, 2 H) 7.61 (s, 1 H) 7.65 (s, 1 H) 7.86 (m, *J*=8.31 Hz, 2 H) 8.12 (m, *J*=8.07 Hz, 2 H) 12.65 (br. s., 1 H). HRMS (TOF) Calculated for $C_{25}H_{23}F_3N_3O_3S^+$ $[M+H]^+$: 502.1407, found: 502.1423.

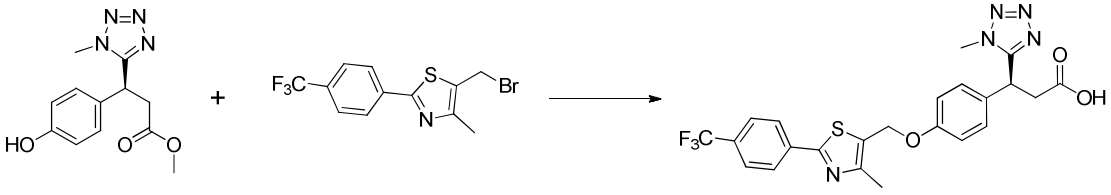
## Synthesis of Compound 8



**5.7** **8**

Compound **8** was prepared according to the procedure of **7** from **5.7**: $^1$H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 8.71 (1 H, s), 8.08 - 8.14 (2 H, m), 7.81 - 7.87 (2 H, m), 7.23 (2 H, m, *J*=8.8 Hz), 7.01 (2 H, m, *J*=8.6 Hz), 5.31 (2 H, s), 4.63 (1 H, dd, *J*=8.9, 6.5 Hz), 3.48 (3H, s), 3.24 (1 H, dd, *J*=16.6, 9.0 Hz), 2.87 (1 H, dd, *J*=16.8, 6.2 Hz), 2.46 (3 H, s). HRMS (TOF) Calculated for $C_{24}H_{22}F_3N_4O_3S^+$ $[M+H]^+$: 503.1359, found: 503.1372.

## Synthesis of Compound 9



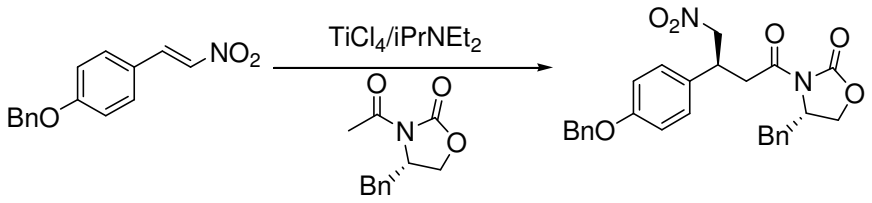

**6.3** **9**

To a solution of compound **6.3** (274 mg, 1.04 mmol) in DMF (10 mL) was added 5-(bromomethyl)-4-methyl-2-(4-(trifluoromethyl)phenyl)thiazole (386 mg, 1.15 mmol), followed by cesium carbonate (374 mg, 1.15 mmol) at room temperature. The resulting mixture was stirred overnight at room temperature, quenched with water and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel flash chromatography (0-100% EtOAc/hexane) to afford methyl ester of compound **9** (485 mg, 0.94 mmol, 90%) as a yellow oil. MS ESI (pos.) m/e: 518 (M+H).

To a solution of the methyl ester (485 mg, 0.94 mmol) in 3:1 THF/EtOH (25 mL) was added 1 N aqueous NaOH (10 mL). The resulting mixture was stirred overnight at room temperature, quenched with 1 N aqueous HCl to adjust the pH to pH7. The resulting solution was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel flash chromatography (0-20% dichloromethane in methanol) to afford compound **9** (300 mg, 63%). MS ESI (neg.) m/e: 502 (M-H). $^1$H NMR (500 MHz, chloroform-*d*) δ ppm 8.02 (2 H, m, *J*=8.3 Hz), 7.69 (2 H, m, *J*=8.3 Hz), 7.19 (2 H, m, *J*=8.7 Hz), 6.95 (2 H, m, *J*=8.7 Hz), 5.18 (2 H, s), 4.56 (1 H, dd, *J*=8.9, 6.0 Hz), 3.84 (3 H, s), 3.61 (1 H, dd,

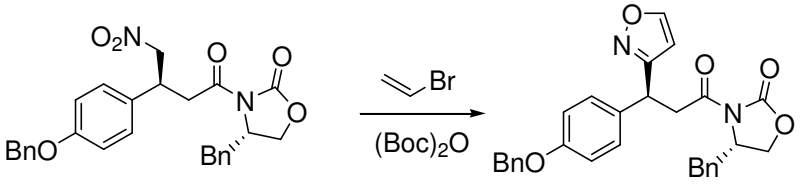
*J*=17.4, 9.0 Hz), 3.08 (1 H, dd, *J*=17.4, 5.6 Hz), 2.51 (3 H, s). HRMS (TOF) Calculated for $C_{23}H_{21}F_3N_5O_3S^+$ $[M+H]^+$: 504.1312, found: 504.1331.

## Synthesis of Compound 10




**10.1** **10.2** **10.3**

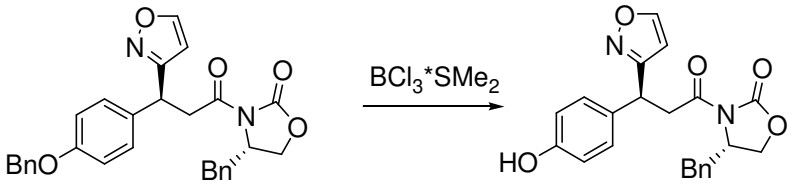
**(S)-4-Benzyl-3-((S)-3-(4-(benzyloxy)phenyl)-4-nitrobutanoyl)oxazolidin-2-one (10.3)**. $TiCl_4$ (43 mL, 1.0 M solution in DCM) was added slowly to a mixture of **10.2** (8.55 g, 39 mmol, commercially available from Aldrich) in DCM (200 mL) at -78 ºC, followed by slow addition of $iPrNEt_2$ (8.14 mL, 46.8 mmol). The mixture was stirred at –78 ºC for 45 minutes and then a mixture of **10.1** (9.95 g, 39 mmol, commercially available from Aldrich) in DCM (40 mL) was added over 15 minutes. $TiCl_4$ (39 mL, 1.0 M solution in DCM) was then added to the reaction. During all the additions, the internal temperature was kept below -72 ºC. The mixture was stirred at –78 ºC for another 4 hours before it was slowly warmed to -10 ºC and then quenched by adding $NH_4Cl$ (saturated 100mL). The organic layer was separated, washed with brine, dried, and concentrated. The crude product was taken into hot MeOH (700mL). The mixture was stirred vigorously at 75 ºC for 3 hours. The mixture was then cooled to room temperature and allowed to stand for 3 hours. The solid product was collected by filtration and washed with MeOH. The product **10.3** (8.5 g, 53%) had a d.e. >99%. MS ESI (pos.) m/e: 475 (M+H). $^1H$ NMR ($CDCl_3$) δ 7.40(m, 8H), 7.28(m, 4H), 6.97(d, 2H), 5.05(s, 2H), 4.63(m, 3H), 4.17(m, 3H), 3.53(dd, 1H), 3.34(dd, 1H), 3.28(dd, 1H), 2.75(dd, 1H).




**10.3** **10.4**

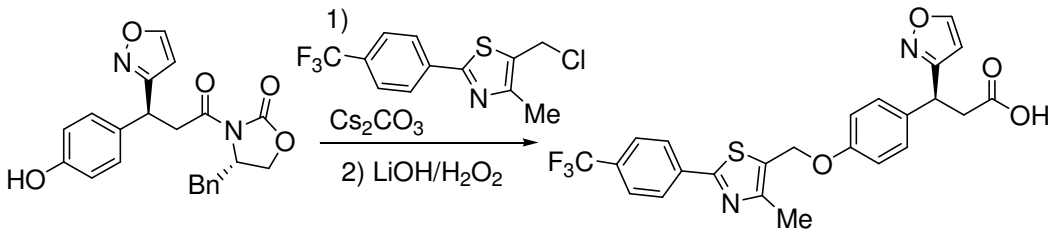
**(S)-4-Benzyl-3-((S)-3-(4-(benzyloxy)phenyl)-3-(isoxazol-3-yl)propanoyl)oxazolidin-2-one (10.4).** $(Boc)_2O$ (6.9 g, 31.65 mmol) was added at room temperature to a solution of **10.3** (10 g, 21.1 mmol), vinyl bromide (230 mL, 1.0 M solution in THF), DMAP (256 mg, 2.1 mmol), and TEA (3.5 mL, 25.3 mmol). The mixture was stirred at room temperature for 2.5 days. During

the reaction, more $(Boc)_2O$ (2 g twice) was added. After HPLC indicated that all **10.3** was consumed, the reaction mixture was taken into EtOAc (500 mL), and saturated sodium bicarbonate (400 mL) was added. The organic layer was separated, washed with brine, dried, and concentrated under vacuum. The crude product was taken into hot MeOH (70 mL). The mixture was stirred vigorously at 75 ºC for 5 hours. The mixture was then cooled to room temperature and allowed to stand for 3 hours. The solid product was collected by filtration and washed with MeOH to give **10.4** (9.5 g, 93%). MS ESI (pos.) m/e: 483 (M+H). $^1$H NMR ($CDCl_3$) δ 8.30(d, 1H), 7.30(m, 12H), 6.95(d, 2H), 6.15(d, 1H), 5.05(s, 2H), 4.76(dd, 1H), 4.64(m, 1H), 4.15(d, 2H), 4.05(dd, 1H), 3.56(dd, 1H), 3.23(dd, 1H), 2.78(dd, 1H).




**10.4** **10.5**

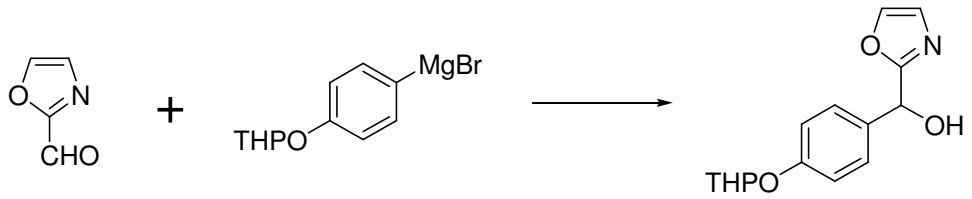
**(S)-4-Benzyl-3-((S)-3-(4-hydroxyphenyl)-3-(isoxazol-3-yl)propanoyl)oxazolidin-2-one (10.5).** Boron trichloride methyl sulfide complex (51 mL, 2.0 M solution in DCM) was added to **10.4** (8.2 g, 17 mmol) in DCM (100 mL) at 0 ºC. After addition, the ice bath was removed, and the mixture was stirred at room temperature for 7 hours. The mixture was cooled in an ice bath and quenched by adding saturated sodium bicarbonate until the mixture was neutralized. More DCM (400 mL) was added, and the organic layer was separated, washed with brine, dried, and concentrated under vacuum. The crude product (6.5 g) was dissolved in 50 mL of hot MeOH. After cooling, the crystallized product was collected by filtration and washed once with MeOH to give **10.5** (4.2 g). The filtrate was concentrated, and the solid that formed was collected and washed to give an additional 1.2 g of compound **10.5** (total 5.4 g, 81%). MS ESI (pos.) m/e: 393 (M+H). $^1$H NMR ($CDCl_3$) δ 8.29(d, 1H), 7.30(m, 3H), 7.20(d, 2H), 7.15(d, 2H), 6.95(d, 2H), 6.14(d, 1H), 4.71(dd, 1H), 4.63(m, 1H), 4.16(d, 2H), 4.00(dd, 1H), 3.54(dd, 1H), 3.21(dd, 1H), 2.76(dd, 1H).




**10.5** **10**

**(S)- 3-(Isoxazol-3-yl)-3-(4-((4-methyl-2-(4-(trifluoromethyl)phenyl)thiazol-5-yl)methoxy)phenyl)propanoic acid (10).** Cesium carbonate (394 mg, 1.21 mmol) was added to a mixture of **10.5** (428 mg, 1.1 mmol) and 5-(chloromethyl)-4-methyl-2-(4-(trifluoromethyl)phenyl)thiazole (319 mg, 1.1 mmol, commercially available from Maybridge) in DMSO (3 mL). The resulting mixture was stirred at room temperature for 2 hours and at 35 °C for 14 hours. After cooling, the mixture was treated with EtOAc (5 mL) and brine (5 mL). The organic layer was separated, washed twice with brine, dried, and concentrated. The crude product (550 mg, 0.85 mmol, 77%) was treated with THF (6 mL) and hydrogen peroxide (30%, 385 mg, 3.4 mmol) and cooled to 0 ºC. $LiOH•H_2O$ (72 mg, 1.7 mmol) in 2 mL of water was added. The resulting mixture was stirred at 0 ºC for 4 hours. The organic solvent was blown away by nitrogen, and the aqueous mixture was acidified by adding HCl (0.6 mL, 3 N). The aqueous mixture was extracted with DCM. The organic layer was dried, concentrated, and purified by flash chromatography to give **10** (220 mg, 53%). MS API-ES m/e: 487.0 (M-H). $^1$H NMR (500 MHz) (DMSO-$d_6$) δ 8.76 (1H, s); 8.13 (2H, d, J=7Hz); 7.86 (2H, m); 7.26 (2H, d, J=6Hz); 7.01 (2H, m); 6.50 (1H, s); 5.23 (2H, s); 4.51 (1H, m); 3.20 (1H, m), 2.80 (1H, m), 2.47 (3H, s). HRMS (TOF) Calculated for $C_{24}H_{20}F_3N_2O_4S^+$ $[M+H]^+$: 489.1090, found: 489.1096.

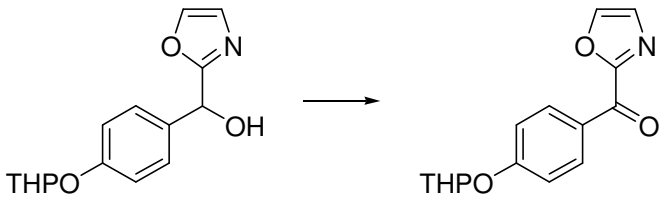
## Synthesis of Compound 11




**11.1**

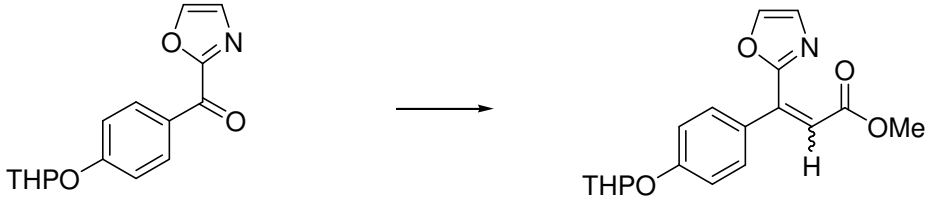
**Oxazol-2-yl(4-(tetrahydro-2*H*-pyran-2-yloxy)phenyl)methanol (11.1).** 4-(2-Tetrahydro-3*H*-pyranoxy)phenylmagnesium bromide (0.5 M in THF, 6.7 mmol) was added dropwise to a solution of oxazole-2-carbaldehyde (5.15 mmol) in THF (8 mL). After stirring at room temperature for 2.5 hours, the reaction was quenched with water, extracted with EtOAc (200 mL), the organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed (silica gel, 1:2 EtOAc/hexane) to obtain compound **11.1** (3.1 mmol, 60%). MS ESI (pos.) m/e:276(M+H). $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 8.02 (s, 1H); 7.31 (d, J=8.7 Hz, 2H); 7.14 (s, 1H); 6.97-7.01

(m, 2H); 6.27 (d, J=5 Hz, 1H); 5.74 (d, J=5 Hz, 1H); 5.44 (s, 1H); 3.74 (m, 1H); 3.52 (M, 1h); 1.72-1.81 (m, 3H); 1.52-1.60(m, 4H).



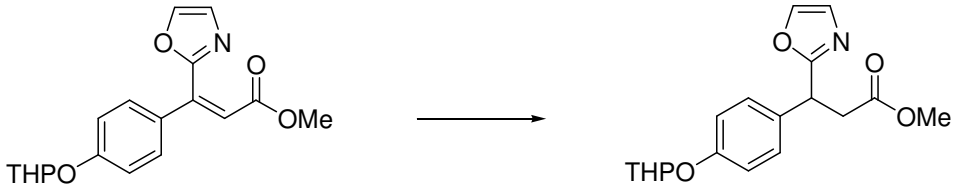

**11.1** **11.2**

**Oxazol-2-yl(4-(tetrahydro-2*H*-pyran-2-yloxy)phenyl)methanone (11.2).** PCC (14.5 mmol, 20%w/w on silica gel) was added to a solution of **11.1** (2.91 mmol) in DCM (20 mL). After 1 hour, the reaction mixture was chromatographed (silica gel, 1:2 EtOAc/hexane) to obtain compound **11.2** (2.41 mmol, 83%). MS ESI (pos.) m/e: 296.0 (M+Na). $^1$H NMR (500 MHz) (DMSO-$d_6$) δ 8.52 (s, 1H); 8.43 (d, J=9 Hz, 2H); 7.67 (s, 1H); 7.23 (d, J=9 Hz, 2H); 5.71 (m, 1H); 3.74-3.76 (m, 1H); 3.62-3.65 (m, 1H); 1.88-1.91 (m, 2H); 1.81-1.82 (m, 1H); 1.59-1.67 (m, 3H).



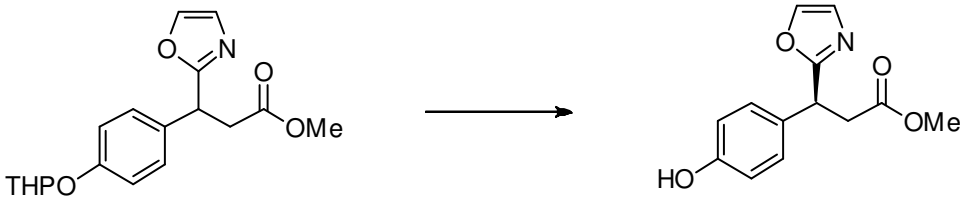

**11.2** **11.3**

**Methyl 3-(oxazol-2-yl)-3-(4-(tetrahydro-2*H*-pyran-2-yloxy) phenyl)acrylate (11.3).** Lithium bis(trimethylsilyl)amide (3.46 mmol, 1M in THF) was added dropwise to a solution of methyl trimethylsilylacetate (3.46 mmol) in THF (5 mL) at –78 °C. After 20 minutes at -78 °C, a solution of **11.2** (2.16 mmol) in THF (9 mL) was added dropwise and the reaction was maintained at -78 °C for 1.5 hours. The reaction was quenched with water and extracted with EtOAc. The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed (silica gel, 1:1 EtOAc/hexane) to afford compound **11.3** (2.55 mmol, 74%). MS ESI (pos.) m/e 330.1 (M+1).



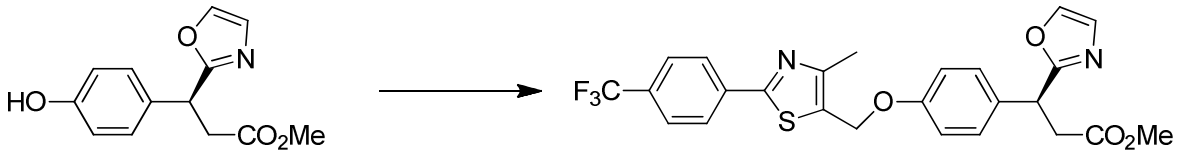

**11.3** **11.4**

**Methyl 3-(oxazol-2-yl)-3-(4-(tetrahydro-2*H*-pyran-2-yloxy) phenyl)propanoate (11.4**). A mixture of compound **11.3** (2.55 mmol) and Pd-C (440 mg) in MeOH was stirred under hydrogen at room temperature for 30 minutes. The Pd-C was removed by filtration through silica gel with EtOAc as eluant. After concentration, the residue was chromatographed (silica gel, 1:1 EtOAc/hexane) to afford compound **11.4** (2.32 mmol, 91%). MS ESI (pos.) m/e 332.2 (M+1).



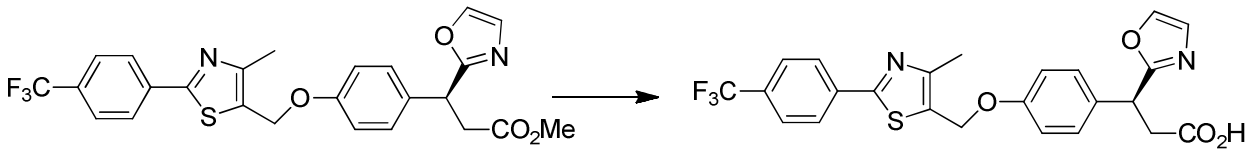

**11.4** **11.5**

**(*S*)-Methyl 3-(4-hydroxyphenyl)-3-(oxazol-2-yl)propanoate (11.5**). A mixture of compound **11.4** (2.1 mmol), *p*-toluenesulfonic acid monohydrate (0.57 mmol) in MeOH (15 mL) was stirred at room temperature for 1.5 hours. After quenching with saturated aqueous $NaHCO_3$, MeOH was removed under reduced pressure. The residue was extracted with EtOAc, and the combined organic extracts were washed with saturated brine, dried over anhydrous sodium sulfate, and filtered through short plug of silica gel. After concentration, the residue was separated by chiral chromatography (OD-H column, 10% i-PrOH/hexane as elution solvent) and compound **11.5** (first peak, 1.0 mmol, 45%) was obtained. MS ESI (pos.) m/e 248.1 (M+1). $^1$H NMR (500 MHz) (DMSO-$d_6$) δ 9.04 (s, 1H); 7.99 (s, 1H); 7.14 (s, 1H); 7.05 (m, 2H); 6.72 (m, 2H); 4.49-4.52 (m, 1H); 3.57 (s, 1H); 3.22-3.27 (m, 1H); 2.89-2.94 (m, 1H).




**11.5** **11.6**

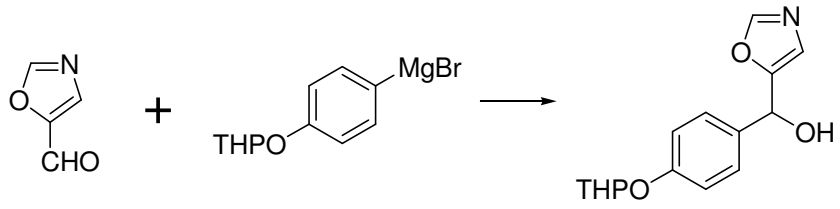
A mixture 5-(bromomethyl)-4-methyl-2-(4-(trifluoromethyl)phenyl)thiazole (0.185 mmol), Compound **11.5** (0.154 mmol) and $Cs_2CO_3$ ( 0.385 mmol) in DMF (4ml) was stirred at room temperature overnight. Then the reaction mixture was diluted with EtOAc (120ml) and washed with brine, dried over anhydrous sodium sulfate. After concentration,the residue was purified by combiflash. Compound **11.6** was obtained in 100% yield. MS ESI (pos.) m/e: 503.0 (M+H).




**11.6** **11**

A mixture of compound **11.6** (0.15 mmol) and LiOH in ethanol and water was stirred at room temperature for 5 hrs. It was acidified with 1N HCl to pH 1-2 and extracted with EtOAc. The organic phase was washed with brine, dried over anhydrous sodium sulfate. After concentration compound **11** (0.09 mmol) was obtained in 60% yield. MS ESI (neg.) m/e: 487.1 (M-H). $^1$H NMR (500MHz) (DMSO-$d_6$) δ (ppm): 1.04(d, J=6 Hz, 3H), 2.46(s, 3H), 2.80 (m, 1H), 3.15 (m, 1H), 4.50 (m, 1H), 5.31(s, 2H), 6.99(d, J=9 Hz, 2H), 7.12 (s, 1H), 7.20 (d, J=9 Hz, 2H), 7.84(m, 2H), 7.96 (s, 1H), 8.11(d, J=8 Hz, 2H), 12.25(s, 1H). HRMS (TOF) Calculated for $C_{24}H_{20}F_3N_2O_4S^+$ $[M+H]^+$ : 489.1090, found: 489.1097.

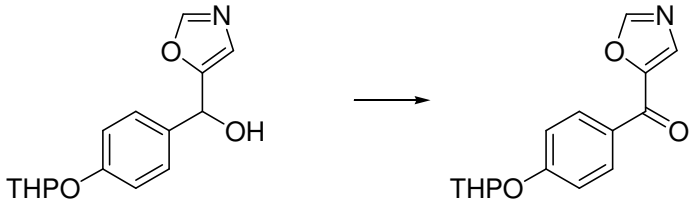
## Synthesis of Compound 12




**12.1**

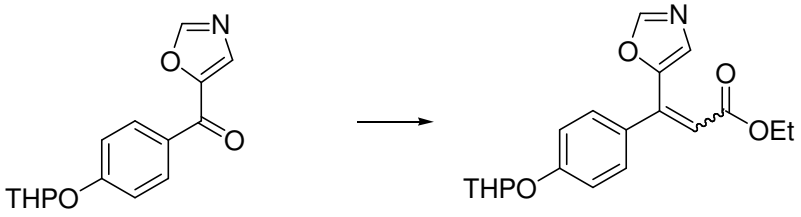
**Oxazol-5-yl(4-(tetrahydro-2H-pyran-2-yloxy)phenyl)methanol (12.1).** 4-(2-Tetrahydro-3*H*-pyranoxy)phenylmagnesium bromide (120 mL, 0.5 M in THF, 60 mmol) was added dropwise to a solution of oxazole-4-carbaldehyde (4.85 g, 50 mmol) in THF (90 mL) at –78 °C. After stirring –78 °C for 21 hours, the reaction was quenched with saturated $NH_4Cl$ (aq) and warmed to r.t.. The mixture was extracted with EtOAc (500 mL), the organic phase was washed with

water, brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 17g of the crude product **12.1**, which was used in the next reaction without further purification.



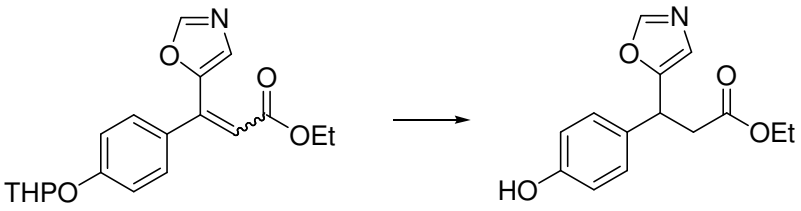

**12.1** **12.2**

**Oxazol-5-yl(4-(tetrahydro-2H-pyran-2-yloxy)phenyl)methanone (12.2).** Dess-Martin periodinane (25g, 60 mmol) was added to a solution of **12.1** (17g crude, ~50 mmol) in DCM (200 mL). After 1 hour, the reaction mixture was concentrated with silica gel and chromatographed (silica gel, 1:2 EtOAc/hexane) to obtain compound **12.2** (5.74g, 21 mmol, 42%, two steps). MS ESI (pos.) m/e: 274.1 (M+H).



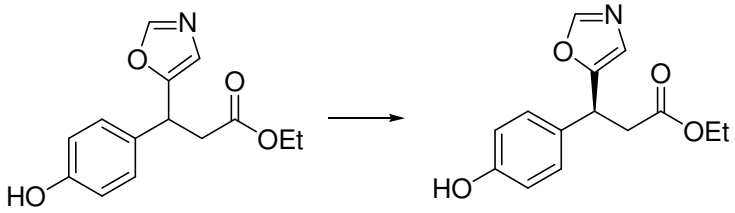

**12.2** **12.3**

**Ethyl 3-(oxazol-5-yl)-3-(4-(tetrahydro-2H-pyran-2-yloxy)phenyl)acrylate (12.3).** To a solution of lithium bis(trimethylsilyl)amide (31.5 mmol, 1M in THF) was added ethyl trimethylsilylacetate (31.5 mmol) dropwise at -78 °C. After 20 minutes at -78 °C, a solution of **12.2** (21 mmol) in THF (60 mL) was added dropwise and the reaction was maintained at -78 °C for 1.5 hours. The reaction was quenched saturated $NH_4Cl$ (aq) and warmed to r.t.. The mixture was extracted with EtOAc (500 mL), the organic phase was washed with water, brine, dried over anhydrous sodium sulfate, filtered, and concentrated with silica gel under reduced pressure. The residue was chromatographed (silica gel, 1:1 EtOAc/hexane) to afford compound **12.3** (4.83 g, 14 mmol, 67%). MS ESI (pos.) m/e: 344.2 (M+H).



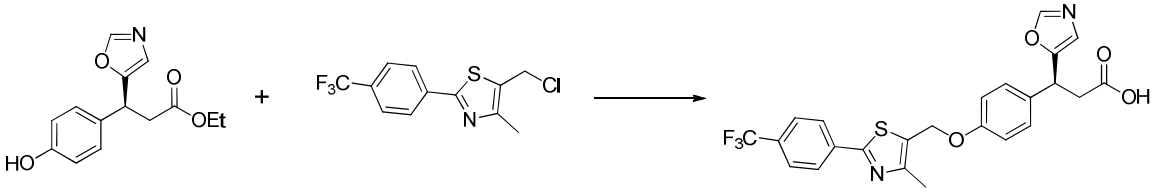

**12.3** **12.4**

**Ethyl 3-(4-hydroxyphenyl)-3-(oxazol-5-yl)propanoate (12.4**). Trifluoroacetic acid (10 mL) was added to a solution of **12.3** (14 mmol) in dry DCM (100 mL) and stirred at room temperature for 2 hours. To the reaction mixture was slowly added solid $NaHCO_3$ with stirring, washed with saturated $NaHCO_3$ (2X), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was then re-dissolved in EtOH, stirred with Pd-C (1.48 g, 0.7 mmol) under hydrogen at room temperature for 14 hours. The Pd-C was removed by filtration through celite with EtOAc as eluant. After concentration, the residue was chromatographed (silica gel, 1:1 EtOAc/hexane) to afford compound **12.4** (1.3 g, 5 mmol, 35%). MS ESI (pos.) m/e 262.1 (M+H).




**12.4** **12.5**

**(S)-Ethyl 3-(4-hydroxyphenyl)-3-(oxazol-5-yl)propanoate (12.5).** Racemic compound **12.4** (1.3 g, 5 mmol) was separated on a semi-preparatory chiral CHIRALCEL OJ-H column (30x250mm), using 20% i-PrOH in hexane as eluant. Eluant containing the peak with greater retention time was concentrated and compound **12.5** (620 mg, 2.38 mmol, 95%) was obtained as off-white solid. The absolute configuration was assigned by analogy to other GPR40 agonist compounds. MS ESI (pos.) m/e: 262.1 (M+H).




**12.5** **12**

**(S)-3-(4-((4-Methyl-2-(4-(trifluoromethyl)phenyl)thiazol-5-yl)methoxy)phenyl)-3-(oxazol-5-yl)propanoic acid (12).** The phenol **12.5** (26 mg, 0.1 mmol) was dissolved in 1 mL of DMF and 5-(chloromethyl)-4-methyl-2-(4-(trifluoromethyl)phenyl)thiazole (35 mg, 0.12 mmol, Matrix Scientific) was added followed by cesium carbonate (49 mg, 0.15 mmol). The reaction was stirred for 16 hours. 1 N LiOH (aq) (1 mL, 1 mmol) was added and the resulting mixture was stirred at 50 °C for 5 hours. The mixture was added with 0.6 mL of 2 N HCl (aq) and 2 mL of DMF. Filtered and purified by HPLC (C18 column, eluted with 10-95% $CH_3CN$ in Water, with 0.1% TFA) to afford Acid **12** (26 mg, 0.53 mmol, 53% yield over two steps) as a white solid. $^1$H NMR (400 MHz, *DMSO-$_{d6}$*) δ ppm 12.30 (1 H, br. s.), 8.20 (1 H, s), 8.12 (2 H, m, *J*=8.2 Hz), 7.84 (2 H, m, *J*=8.2 Hz), 7.23 (2 H, m, *J*=8.6 Hz), 7.00 (2 H, m, *J*=8.6 Hz), 6.95 (1 H, s), 5.32 (2 H, s), 4.46 (1 H, t, *J*=7.7 Hz), 3.01 (1 H, dd, *J*=16.0, 7.8 Hz), 2.85 (1 H, dd, *J*=16.0, 7.8 Hz), 2.46 (3 H, s). $^{13}$C NMR (400 MHz, *DMSO-$d_6$*) δ ppm 171.94, 163.33, 156.74, 153.90, 151.85, 151.34, 133.30, 128.93, 128.77, 126.60, 126.20, 121.64, 115.02, 61.58, 38.57, 37.76, 15.06. HRMS (TOF) Calculated for $C_{24}H_{20}F_3N_2O_4S^+$ $[M+H]^+$ : 489.1090, found: 489.1095.